REMARKS

Favorable reconsideration is respectfully requested in view of the following remarks.

I. CLAIM STATUS

Claims 24-35 are pending in this application and stand rejected.

II. SCOPE OF ENABLEMENT REJECTION

On pages 2-4 of the Office Action, claims 30-35 were newly rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification, while being enabling for a method for preventing recurrence of liver cancer for five years, does not reasonably provide enablement for a method for preventing recurrence of cancer in general for five years.

This rejection is respectfully traversed.

The test of enablement is whether one reasonably skilled in the art could make or use the invention based on the disclosure in the specification coupled with the knowledge in the art without undue experimentation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See M.P.E.P. § 2164.01.

On pages 2-3 of the Office action, it was indicated that the claims are directed to preventing recurrence of any cancer and one skilled in the art cannot extrapolate the teachings of the disclosure to the scope of the claims, because different cancers have different etiologies and characteristics. The Office contends that one skilled in the art cannot predict whether different cancers would have the same response to the same drugs. The Office cited Montesano (1996), Burmer (1991) and Busken (2003) as allegedly supporting this position.

It is respectfully submitted that the cited references do not support the position that the skilled artisan cannot predict whether different cancers would have the same response to the

same drugs. The cited references simply do not teach or suggest this. Nor do the references teach or suggest methods for preventing recurrence of cancer by administering activated lymphocytes in combination with a surgical procedure to prevent the recurrence of the cancer for at least five years as in the claimed invention. Instead, the cited references merely relate to a discussion about the different etiologies and different genetic constitutions for various cancers. Thus, it is respectfully submitted that the cited references fail to support to the Offices' position regarding the unpredictability in the art.

Moreover, there have been numerous reports that activated lymphocytes have an anti-tumor effect for various types of cancers. To be more specific, activated lymphocytes are known to have therapeutic effects for: (1) brain cancer (Yamazaki et al., Neurol Med Chir, 32, 255-261 (1992)), (2) advanced ovarian cancer (Takeda et al., J Jpn Soc Cancer, 30, 967-971 (1995)), (3) malignant melanoma (MM) (Yamazaki et al., BCG Immunotherapy Journal, 15, 51-55 (1991)), and (4) liver cancer (Takayama et. al., Cancer, 68, 2391-2396 (1991)), by way of example only.

Furthermore, the lymphocytes of the claimed invention are activated antigen nonspecifically by stimulation with anti-CD3 antibody and IL-2. Consequently, the activated lymphocytes can react to various kinds of cancer and are not limited to a specific cancer. In other words, the activated lymphocytes have reactivity (poly-specificity) to not only a specific cancer, but a variety of other cancers.

Therefore, the fact that the activated lymphocytes of the claimed invention are effective in preventing recurrence of one type of cancer also suggests that they have an effect of depressing recurrence of other cancers.

In addition, it is well established that anti-cancer drugs, such as nimustine, which has been used to treat glioblastoma in the United States and Japan, are capable of treating a wide variety of cancers, such as, rectal cancer, gastric cancer, bronchogenic cancer, malignant lymphoma and hepatic cancer (Gan To Kagaku Ryoho, Cancers and Chemotherapeutics, 13(7): 2363 (1986)). Similarly, it is known that fluorouracil (5FU) has been applied for treating brain

cancer, hepatic cancer and colon cancer even though there is no specific trait common to these cancers to which the anti-cancer drug is applicable.

Accordingly, it does not necessarily follow that different cancers cannot be treated with the same anti-cancer drug as postulated by the Office.

Liver cancer and glioblastoma are obviously different from each other. However, if nimustine is applicable to glioblastoma and hepatic cancer as indicated by the Examiner, there would be common traits relevant to the liver cancer and glioblastoma in a development process thereof. However, the most important factor in developing cancer therapeutics is that the anti-cancer drug brings about medical effects, such as curing the patient of cancer, reducing the cancer or suppressing the recurrence of the cancer for a certain period to prolong the life of the patient, regardless of the medical process applied and whether the cancer cells react to the drug in like manner.

Again, it has been observed that nimustine, which is widely used for treating hepatic cancer, bronchogenic cancer and brain cancer has the effect of pathologic complete response to a variety of cancers.

Based on the above, there is no reasonable basis for asserting that the claimed lymphocyte therapy would not be effective for treating various kinds of cancer as claimed.

Furthermore, all the references cited by the Examiner are concerned with mutation or polymorphism of a specific gene. In chemotherapy, the effect of an anti-neoplastic drug changes with one gene mutation has been known. However, the specificity of activated lymphocytes having poly-specificity retains extensive responsiveness to a variety of cancers.

It has been disclosed that Sekine became aware of a significant difference in recurrence-free survival rate from 6 months to 17 months after a therapeutic procedure during the course of treatment of preventing recurrence of cancer, but the effect of preventing recurrence of the cancer is lost in the second year after the therapeutic procedure. Therefore, it would not have

been obvious to predict that the effect of preventing recurrences of cancer can be seen one more time in the fifth year.

Therefore, in contrast to the Office's position, it is respectfully submitted that the claimed invention is effective for treating various kinds of cancer.

In view of the above, the rejection of claims 30-35 under 35 U.S.C. § 112, first paragraph, is untenable and should be withdrawn.

III. OBVIOUSNESS REJECTION

On pages 4-7 of the Office Action, claims 24-35 remain rejected under 35 U.S.C. § 103(a) as obvious over Sekine et al. (Human Cell, Vol. 7, No. 3, pp. 121-124 (1994)) in view of Sasaki et al. (J. of HBP Surgery, Vol. 5, pp. 14-17 (1998)).

This rejection is respectfully traversed.

The claimed invention relates to methods for preventing recurrence of liver cancer and cancer in general by administering activated lymphocytes in combination with a surgical procedure to prevent the recurrence of the cancer for at least five years.

As argued in the response filed July 5, 2005, Sekine and Sasaki fail to disclose a method resulting in the prevention of recurrence of liver cancer or cancer in general for at least five years. This is acknowledged in the paragraph bridging pages 3-4 of the Office Action of March 3, 2005, wherein it is indicated that "Sekine et al. do not teach prevention of recurrence of cancer for five years."

As argued in the last response, Sekine discloses that significant differences were shown in recurrence rate among the groups from 6 months to 17 months post-therapy, whereas FIG. 3, which shows the recurrent-free survival, proves that no significant difference of the groups thereafter was recognized. See the 10th line from the bottom of page 122 of Sekine. Therefore, it is again respectfully submitted that the claimed method of preventing recurrence of liver cancer and cancer in general by administering activated lymphocytes in combination with a surgical

procedure to prevent the recurrence of the cancer for at least five years could not have been suggested from the teachings in Sekine.

In reply to this argument, on page 5 of the Office Action, it was argued that while Sekine only teaches prevention of reoccurrence of liver cancer for two years, it would have been expected that Sekine's method would prevent recurrence for five years in view of Sekine's teaching that higher preventative effect could be obtained if the infusion was carried out more frequently and continuously after an operation. The Office relies on the first paragraph under the conclusion on page 7 of Sekine.

On page 6, it was indicated that the prevention of the recurrence of liver cancer for five years amounts does not amount to surprising and unexpected results as argued by Applicants. Specifically, it was indicated that the 3rd year recurrence rate in Sekine of 70% corresponds to a 30% survival rate of not having recurrent liver cancer.

However, it is respectfully submitted that there is no reasonable basis for the Office to extrapolate a 5 year survival rate from a 3rd year recurrence rate.

Again, it appears that the Office has confused the term "overall survival" with the term "recurrence-free survival" (disease-free survival) in its analysis of Sekine. See also pages 3-4 on the July 5, 2005 response. It is respectfully submitted that these terms are defined differently in the art.

For instance, the website (http://www.breastcancer.org/dictionary/overallsurvival_t.html) defines the term "overall survival" as:

> The percentage of people in a study who have survived for a certain period of time, usually reported as time since diagnosis or treatment. Often called the survival rate.

Also, the website (http://www.prostate-cancer.com/prostate-cancer-glossary/biochenical-recurrence-free-survival.html) defines the term "recurrence free survival" as:

> Biochemical Recurrence Free Survival means that after undergoing a prostate cancer treatment the patient's PSA level does not rise for 2 to 3 consecutive years.

> Biochemical relapse free survival should not be confused with overall survival. Overall survival, when used in a clinical sense, refers only to those who did not die as a result of their prostate cancer at the time of follow-up. Many doctors believe that there is comparative difference in the overall survival rates, possibly due to the unusually slow growth rate common in most types of prostate cancers.
>
> Biochemical relapse free survival is a more specific term. The word biochemical refers to the use of the prostate-specific antigen as a tumor marker. If the patient relapses biochemically, his PSA level has risen significantly. Generally, patients who undergo a prostate cancer treatment should have nearly undetectable PSA levels, somewhere around or under 1.0 ng/mL. Those with a high PSA velocity after treatment have experienced biochemical relapse, but they have not died Biochemical relapse, however, is a reasonable indicator of who will develop recurrent prostate cancer.

Thus, it is clear that the art does not consider the term "overall survival" to be the same as "recurrence-free survival."

Nonetheless, in the fifth paragraph on page 5 of the Office Action, it was indicated that:

> Although Sekine only teaches prevention of recurrence of liver cancer for two years, one would have expected that the method of Sekine et al., using activated lymphocytes would prevent recurrence of liver cancer for five years.

However, recurrence could be significantly suppressed for 6 to 17 months as disclosed in the reference published by Sekine, but a significant difference was not manifested, and consequently, it is less effective in preventing recurrence. Since the recurrence preventing effect in Sekine disappears at the second year, it would be difficult for one of ordinary skill in the art to predict the recurrence preventing effect after five years. As such, there is no suggestion in Sekine and the reference lacks a reasonable expectation of success of arriving at the claimed invention.

Also, in the fifth paragraph on page 5 of the Office Action, it was indicated that:

> In view of the teaching of Sekine et al. that from previous experimental administration, they knew that higher preventive effect could be obtained if the infusion were carried out more frequently and continuously after an operation, and

> that the currently used dosage is a minimum dosage (p. 7, first paragraph under conclusion). It is noted that to determine optimum concentration of reactants is within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425.

However, Applicants respectfully submit that hyperstimulation can lead to immunologic unresponsiveness in the case of immune reaction, whereby such treatment becomes less responsive. In other words, it cannot be determined with a reasonable degree of success whether multi-cycle treatment provides a therapeutic benefit to activation of the immune reaction. Thus, in contrast to the Office's position, the applied dosage cannot be routinely optimized as alleged in the Office Action. Instead, dosage should be determined after confirmation of the effect and safety, and it cannot otherwise be determined by one of ordinary skill in the art.

At the top of page 6 of the Office Action, it was indicated that:

> Further some recurrent liver cancer is not fatal, and would not be counted in over-all survival rate, and thus not all patients in over-all survival group are expected to have recurrent liver cancer, in view of the teaching of Sekine et al that out of 52 cases, there are 22 recurrence cases and 6 deaths in the second year (abstract). Thus in view that liver cancer patients with hepatectomy alone could survive not only 5 years at a rate of 32% , but even 10 years at a rate of 23% for patient having bad liver function at the time of surgery, as taught by Sasaki et al, one would have expected that some patients having hepatectomy and treated with activated lymphocytes, as taught by Sekine et al, would not have recurrent liver cancer for at least 5 years.

However, the objective of the present invention is essentially to provide "a recurrence depression effect by administration of lymphocytes" to reduce the rate of recurrence of liver cancer in comparison with the control group (non-administered group). The lymphocyte administered group suppressed the recurrence significantly ($P<0.01\%$) after five years, compared to the control group. Applicants respectively submit that it cannot definitively be said that the recurrence after five years can be suppressed by a combination of Sasaki and Sekine. More specifically, since recurrence could not significantly be suppressed after at least two years, one of

ordinary skill in the art could not determine if recurrence could be significantly suppressed after five years.

In other words, as argued in the previous response, the Office's position regarding the expected 5-year survival is inconsistent with the high recurrence rates disclosed in Sekine. Again, Sekine discloses that the recurrence rate for liver cancer is 33% in the first year, 57% in the second year, 70% in the third year, and that no effective preventative method is known. In this sense, Sekine teaches away from the claimed method of prevention for 5 years. As such, based on the teachings of Sekine and the general knowledge in the art, no reasonable expectation of success existed at the time of the publication of Sekine for the prevention of recurrence of liver cancer or cancer in general for five years.

In contrast, the Applicants first discovered that activated lymphocytes can surprisingly prevent cancer recurrence in liver cancer patients for five years after treatment

In reply to this position, the Office at the middle of page 6 of the Action argued:

> Moreover, contrary to Applicant's argument, Sekine does not teach away from the claimed method for prevention for 5 years. The expected 5-year survival of 32% (at) is not inconsistent with the high recurrence rates disclosed in Sekine, which is 33% for recurrence of liver cancer in the first year, 57% in the second year and 70% in the third year because they are data at from different year, and because for the third year, 70% with recurrent liver cancer means 30% would not have recurrent liver cancer, and thus at least 30% or more ere survival, when considering not all recurrent liver cancers are fatal.
>
> (*) This is thought to be 5 year survival rate of liver malfunction group of Stage II in Figure 3 of the cited Sekine et al reference.

As to the Office's view that 70% with recurrent liver cancer (not recurred by 30%) means 30% would not have recurrent liver cancer after 3 years relative to the 5-year survival of 32% in the cited Sasaki, it is noted that HCC in Sasaki is analyzed as being grouped into Stage I , Stage II (good hepatic function group), Stage II (liver malfunction group), Stage III, and Stage IV.

On the other hand, an observational study is made with respect to groups for Stage I, Stage II, Stage IIIa, Stage IVa in Sekine (cf. Table 1 in the Lancet reference by the same author). The subjects to be analyzed in the Sekine study are different from those in Sasaki. Consequently, it would be difficult to compare both cases in the Sekine and Sasakai references with each other. To simply this analysis, the cases in Sekine and Sasaki can be enumerated in the following Table. As can be seen from this reference Table, both the cases cannot thoroughly be compared due to discrepancy in stage measure.

	Stage I/I1	Stage III/IV
Sekine (Lancet Table I)	53%	47%
Sasaki (Table 1)	77%(21+56)	22%(15+7)

The comparison between both citations can be drawn in survival rate is as follows:

Contents		1st year	2nd year	3rd year	5th year
Sekine et al Reference (Non-administered Group)	General **(Recurrence** Rate)	33%	57%	70%	n/a
	Test Result (Recurrence Rate) (Calculated based on Fig. 3)	40%	49%	n/a	n/a
	Test Result (Mortality Rate)	n/a	11.5% (6/52)	n/a	n/a
Present Invention (Non-administered Group)	**Recurrence-free** Survival Rate	n/a	n/a	n/a	21%
	Recurrence Rate	n/a	n/a	n/a	89%
Sasaki et al Reference	Mortality Rate of Liver Malfunction Group in Fig. 3	6%	17%	28%	68%
	Survival Rate of Liver				

Based on these Tables, it is evident that Sasaki, whose mortality rate is 17%, is undeniably higher in mortality rate than Sekine whose mortality rate at the second year is 11 .5%. Since the survival rate at the fifth year in Sekine is 32%, the recurrence-free survival rate should be less than 32% (this means that it is not fatal even if all liver cancers recur as indicated by the Examiner), which is substantially equal to or less than 21% of recurrence-free survival rate in the present invention (mortality rate at the second year of the present invention is lower than that in Sekine). Thus, Applicants respectfully submit that the Office's position that at least 30% or more equates to survival for five years lacks a reasonable scientific foundation.

Lastly, on page 7 of the Office Action, it was indicated that "[t]he claims are not limited to glioblastoma, and thus they are still obvious in view of the combined teaching in the art."

However, as indicated above in response to the enablement rejection, the activated lymphocytes of the claimed invention have anti-tumor activity against various kinds of cancer. Thus, it should not matter that the claims are not limited to glioblastoma.

Therefore, the rejection of claims 24-35 under 35 U.S.C. § 103(a) is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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